Risk: Risk of Adverse Health Outcomes & Decrements in Performance due to Inflight Medical Conditions

Gap: Med02: We do not have the capability to provide a safe and effective pharmacy for exploration missions.

Responsible Element: Exploration Medical Capability (ExMC)

Status: Open

Rationale for Gap Med02 Research Plan

The Exploration Medical Capabilities (ExMC) Element of NASA's Human Research Program is charged with identifying medical capabilities that can address the challenges of prevention, diagnosis, and treatment of disease and injuries that could occur during exploration missions beyond Earth's orbit. Faced with the obstacle of access to in-flight medical care, and limitations of vehicle space, time, and communications; it is necessary to prioritize what medical consumables are manifested for the flight, and which medical conditions are addressed. Studies of astronaut health establish the incidence of common and high risk medical conditions that require medical intervention during long-duration exploration missions. In 2000, the Institute of Medicine (IOM) convened a committee of experts, Committee on Creating a Vision for Space Medicine during Travel beyond Earth Orbit, to examine the issues surrounding astronaut health and safety for long duration space missions. Two themes run throughout the committee's final report: (1) that not enough is known about the risks to human health during long-duration missions beyond Earth's orbit or about what can effectively mitigate those risks to enable humans to travel and work safely in the environment of deep space and (2) that everything reasonable should be done to gain the necessary information before humans are sent on missions of space exploration (IOM, 2001). Although several spaceflight focused pharmaceutical research studies have been conducted, few have provided sufficient data regarding medication usage or potency changes during spaceflight. The Du pharmaceutical stability study assessed medications flown on space shuttles to and from the International Space Station (ISS) from 2006 until 2008; of which some medications were still viable beyond their expiration dates (Du et al, 2011). However, as with many spaceflight studies, the small 'n' associated with this study limits the ability to draw strong conclusions from it. Dr. Wotring and others have recently published articles containing information regarding medication usage, indications, and efficacy gleaned from spaceflight records (Wotring et al, 2015, 2016; Barger et al, 2014; Basner and Dinges, 2014). Although some conclusions can be drawn from these studies, the inability to fully quantify medication usage, indications, side effects, and effectiveness, limits insight as to which medications should be prioritized for further research.

MED02 Research Plan Assumptions

The results and outcomes based on the recommendations of this Element research plan are limited by regulatory and procurement restraints, and predictive solutions for unknown challenges that may be experienced during a Mars mission expected to occur in the 2030s. Despite these limitations, the Element will proceed with the execution of this research plan with the goal of gathering as much data as possible, and learning as much as possible, to provide a safe and effective pharmaceutical formulary for use during exploration missions.

Overview of the Strategy for Gap Mitigation

The Med02 "Pharmacy" Gap identifies a strategy to ensure that medications used to treat medical conditions during exploration missions are available, safe, and effective. It is clear that pharmaceutical intervention is an essential component of risk management planning for astronaut health care during exploration missions. Filling this Gap requires assembling a formulary that is comprehensive enough to prevent or treat anticipated medical events, and is chemically stable, safe, and robust enough to have sufficient potency to last for the duration of an exploration space mission. In cases where that is not possible, filling this Gap requires exploration of novel drug development techniques, dosage forms, and dosage delivery platforms that enhance chemical stability as well as therapeutic effectiveness.

This research plan will outline the steps, processes, procedures, and research portfolio aimed at identifying a capability that will provide a safe and effective pharmacy for any specific exploration Design Reference Mission (DRM) by addressing seven critical questions:

Question 1: What medications do we think we need for a specific DRM?

Question 2: Of the full set of medications selected for a DRM, which will be effective throughout the journey and which will not?

Question 3: Of the medications that do not remain stable for the full mission duration, can we characterize their likely effective shelf life on a specific DRM?

Question 4: Can we provide the crew a way to determine in real time whether a medication is chemically stable, still active, or degraded?

Question 5: As the formulary medications degrade, will they become toxic? Will they remain safe and effective?

Question 6: Do alternative methods exist for supplying formulary medications for a DRM? Do alternative medications or treatments exist that could be supplied to a DRM?

Question 7: Can we modify existing properties of pharmaceuticals to minimize their resource footprint or improve their tolerance to the spaceflight environment?

The proposed pathway for this research is outlined below in Figure 1.

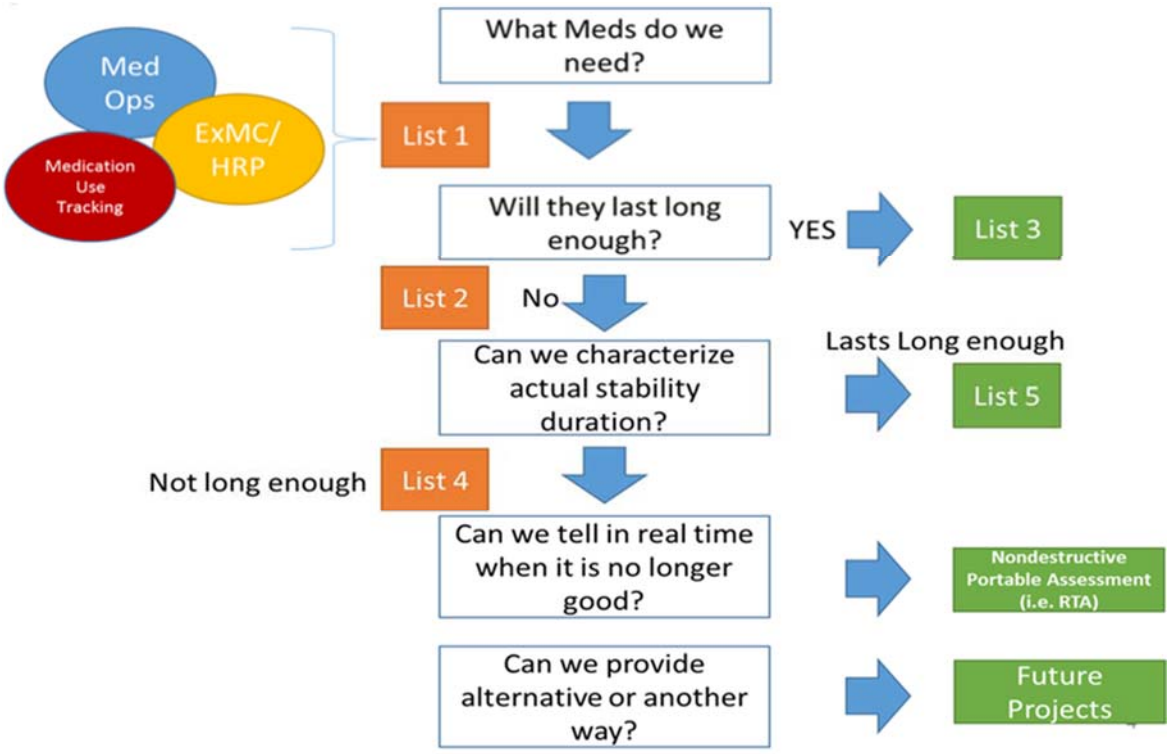

Figure 1: Overview of the proposed pharmacy research pathway.

The research portfolio consists of projects having the potential to lead to significant advances in astronaut health care. However, the research activities aimed at addressing the adverse medical outcomes anticipated during exploration missions focus on needs that differ from those associated with the International Space Station (ISS) and Space Shuttle missions that have formed the basis of our operational experience to date. To address the ExMC Element's Med02 "Pharmacy" Gap, the research focus should be comprehensive across all areas of concern; crosscutting in that it should make use of a body of knowledge and evidence-based models and theories that are continually extended, refined, and revised; translational in that it should focus on expediting the discovery of new tools and treatments by using a multidisciplinary, highly collaborative "bench-to-bedside" approach (Woolf, 2008); and lastly, interventional, by using clinical studies where appropriate to verify the efficacy and safety of targeted treatments or preventive measures.

The proposed approach to building this research portfolio is to seek research projects that concentrate on four major focus areas:

1. Formulary selection (Critical Question 1)
2. Formulary potency and shelf life (Critical Questions 2, 3, and 4)
3. Formulary safety and toxicity (Critical Question 5)
4. Novel technology and innovation such as portable real-time chemical analysis innovative drug therapies and dosage and delivery platforms (Critical Questions 6 and 7).

Target deliverable for closure of gap

A recommendation for a chemically stable, safe, and effective medication formulary that supports the operational needs of exploration space missions by FY2025.

Procurement Mechanism(s): Directed adjunct and supportive research as needed; solicited research projects

Research Plan Development

The Pharmacotherapeutics Discipline has partnered with the ExMC Element to develop and propose this research plan; which outlines the steps, processes, procedures, and research portfolio that will lead to closing the Med02 Gap by 2025 (pink and red flags in Figure 2). This plan will be reviewed and evaluated by a panel of experts from the pharmaceutical industry, regulatory, and academic scientific communities. Comments and recommendations from the expert panel report will be incorporated into the final research plan where applicable. The structured research pathway, as illustrated in Figure 2, is needed to address the aforementioned critical questions, and thereby obtain as much knowledge as possible that will lead towards a safe and effective medication formulary for exploration missions.

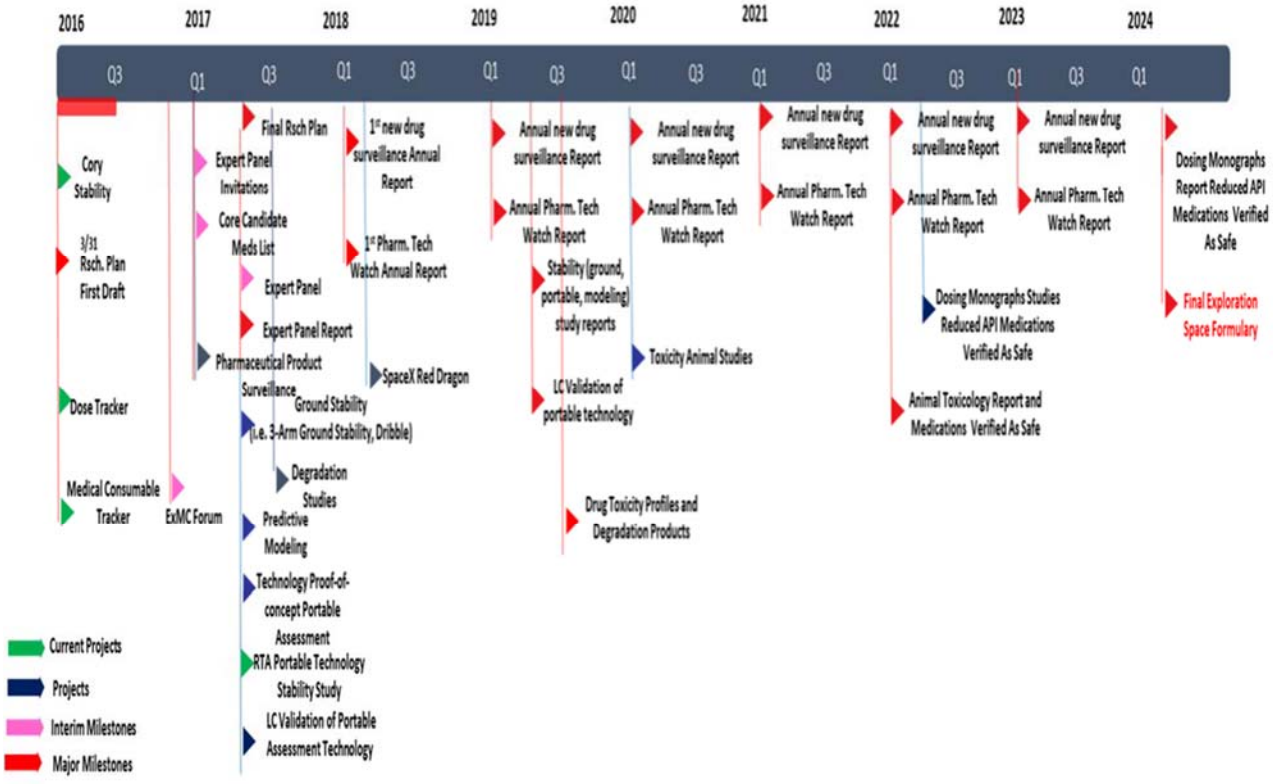

***Figure 2**: Visual description of the ExMC Med02 "Pharmacy" Gap mitigation strategy timeline, which provides a broad overview of the targeted schedule for project initiation (blue flags) and an illustration of project chronology and overlap, while highlighting expected deliverables, shown as interim milestones (pink flags), and major milestones (red flags).*

Deliverables for research plan development

1. The Pharmacotherapeutics Discipline and the ExMC Element develop a draft research plan that defines the steps, processes, procedures, and research portfolio targeted at closing the Med02 Gap by 2020 (end of 2nd Q, FY16).
2. The draft research plan is reviewed by ExMC and Medical Operations stakeholders; the subsequent baseline research plan is presented at the ExMC weekly Forum (beginning of 4th Q, FY16).
3. The baseline research plan is updated in response to feedback from the ExMC Forum (by end of 4th Q, FY16).
4. Solicitations are initiated for recommendations of candidates to participate on the panel of pharmaceutical science experts from the pharmaceutical industry, regulatory agencies, and academia (by end of 4th Q, FY16).
5. The list of prospective expert panelists is vetted by Pharmacotherapeutics and ExMC stakeholders and narrowed down to a list of finalists, who will be sent invitations (1st Q, FY17).
6. The meeting of invited expert panelists convenes to review the baseline research plan (2nd Q, FY17).
7. An expert panel proceedings report is developed; it includes panelist recommendations that will be incorporated into the final research plan (by end of 2nd Q, FY17).

Formulary Selection

Critical Question 1: What medications do we think we need for a specific Design Reference Mission (DRM)?

Exploration space missions pose several challenges to providing a comprehensive medication formulary designed to accommodate the size and space limitations of the spacecraft; while addressing the individual medication needs and preferences of the crew, the negative outcome of a degrading inventory over time, the inability to resupply before expiration dates, and the need to properly forecast the best possible medication candidates to treat conditions that will occur in the future. The NASA Lifetime Surveillance of Astronaut Health (LSAH) proactively collects data on astronaut medical care and workplace exposures, especially those occurring in the training and spaceflight environments, and conducts operational and health care analyses to look for trends in exposure and health outcomes. NASA's Life Sciences Data Archive also includes data from human subjects derived from both past and current spaceflights, as well as data from analog studies. The majority of the medical occurrences that have affected NASA astronauts during previous space missions, and that were captured by the incidence data from the Integrated Medical Model (IMM) update, could be treated or mitigated by medications. Pharmacy needs and medication class recommendations to address the identified medical occurrences will be received from the Concept of Operations (MED01) Team and implemented in the research plan as warranted.

The conceptual design of the exploration mission formulary and the components assembled to construct it is as important as the medication contents themselves. An ideal exploration mission formulary design would have three components (Figure 3). The first component, and largest inventory in the exploration mission formulary, would be the centralized Core Formulary. The Core Formulary would consist of an inventory of medications accessible to all crewmembers, including representative medications from therapeutic classifications targeted at treating common and priority medical events and conditions identified by previous studies, data mining, and scientific literature, and as captured in NASA's and other space agencies' archival data, and those predicted using simulation and modeling technology. Studies have shown that drug compounds are often therapeutically classified according to their chemical structures. It is hypothesized that drugs currently used and future, possibly superior drug compounds from the same therapeutic classifications; will have similar chemical structures and degradation behaviors. Studies have also demonstrated the ability to predict drug indications and drug side effects on the basis of the chemical structure of the drug (Keiser et al., 2009; Scheiber et al., 2009; Atias and Sharan, 2011; Pauwels et al., 2011). Therefore, as opposed to selecting specific medications available today that may become obsolete or replaced by superior medications in the future; a list of therapeutic classifications will be compiled targeting prevention and/or treatment of medical problems anticipated during exploration missions. (Information on medical problems anticipated during exploration missions will be obtained from the Concept of Operations (MED01), ExMC Risk Analysis (MED08), and the Exploration Medical Condition List.) One or two candidate medications from each therapeutic classification that show evidence of exceptional chemical stability and efficacy performance as demonstrated operationally, or in the literature; will be selected for further evaluation for prospective use in an exploration mission Core Formulary. The Core Formulary will be managed in a format similar that of a "Pyxis" delivery system in a hospital, which enables medication use tracking for mission risk assessment. This information will be processed through the Medical Data Architecture (MED07) and the In-Flight Risk Posture (MED09) tools.

The second component of the exploration mission formulary would be a small inventory of personalized medications for each crewmember. The Crewmember Personalized Medicine Component would consist of crewmember-specific maintenance drugs and a few less critical medications (including herbal and nutritional supplements) based on individual crewmember preferences. Selection of crewmember-specific medications will be based on astronaut preference and on the personalized medicine needs of crewmembers. Information from the Pharmacy research pathway will be made available to the Personalized Medicine Gap (MED03) to assist with selection of high-yield medications and to ensure that the operational needs of the exploration DRM are met.

The final component of the exploration mission formulary would be another centralized but smaller inventory of medications dedicated to emergency medicine and designed to address medical conditions or injuries requiring immediate or urgent medical attention.

These medications are considered critical to initial patient stabilization, and require ready accessibility within the medical area of the transit or planetary habitat. Medication selection for this component is also contingent on recommendations from the Concept of Operations (MED01) and the Ethics Research Pathway (MED06).

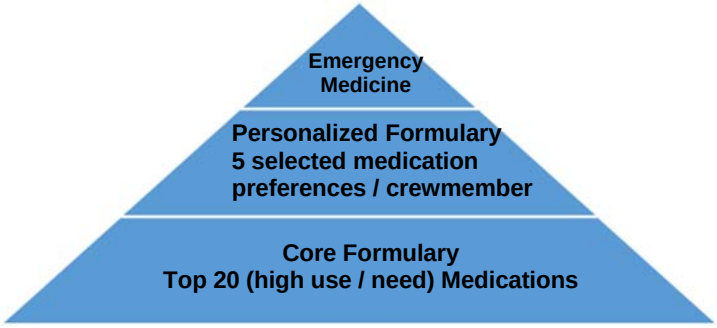

***Figure 3**: The proposed formulary will have three components*:

- *The largest, "Core Formulary," will be a centralized, shared inventory consisting of medications identified as high use or of significant or priority need.*
- *The second will be a smaller, personalized medication inventory containing no more than five chronic condition maintenance or preferred therapies, as selected by each crewmember.*
- *The final component will be a small inventory of crucial emergency medications.*

Deliverables for answering Critical Question 1

1. Element Directed (ExMC Element Scientist, Clinical and Research Pharmacists): A list consisting of candidate medications from targeted therapeutic classifications aimed at addressing medical events anticipated to be experienced during exploration space missions (1st Q, FY17); as suggested by
    a. Apollo, ISS, and Shuttle medical logs, and Mercury and Gemini mission data
    b. The NASA Lifetime Surveillance of Astronaut Health (LSAH)
    c. NASA's Life Sciences Data Archive
    d. Integrated Medical Model (Fig. 4.0)
    e. Medical Optimization Network for Space Telemedicine Resources (MONSTR)
    f. International Space exploration program data
    g. Occupational Health Tracking data as available
    h. Dose Tracker experimental data recorded from flight
    i. Medical Consumables Tracker experimental data recorded from flight
2. Element Directed (Research Pharmacist): Ongoing surveillance of clinical / scientific research, literature, and the approved pharmaceutical industry pipeline to assist with identification of promising Core Formulary medication candidates from the targeted therapeutic classifications aimed at addressing the anticipated medical events (beginning 1st Q, FY17). Drug information sources used:
    a. Pharmaceutical manufacturers
    b. Literature
    c. Research organization data sharing
3. Element Directed (Research Pharmacist, Potomac Institute): An *annual report highlighting promising Core Formulary medication candidates identified from ongoing surveillance activities to the ExMC Element Scientist (1st Q, FY18).

Formulary Potency and Shelf Life

Critical Question 2: Of the full set of medications selected for a DRM, which will be effective throughout the journey and which will not?

a. What are the effects of the deep space environment on medication shelf life with respect to therapeutic effect?

b. Are there alternatives to current formulary selections that would have a sufficient shelf life to last for the duration of an exploration spaceflight mission?

The unique physical and environmental factors (e.g. radiation) of space missions may contribute to the instability of pharmaceuticals. It is of clinical importance to determine whether medications included in an exploration mission formulary would be vulnerable to more rapid degradation precipitated by the radiation environment of deep space. Degradation of pharmaceutical formulations can result in inadequate efficacy and/or untoward toxic effects that may compromise astronaut safety and health. NASA has conducted research to determine whether medications flown in space would remain viable after being exposed to the environmental conditions of spaceflight. Results from those studies suggest that some medications are inherently unstable when exposed to spaceflight conditions. Also, a number of medications showed significant degradation of active drug content after flight relative to matching ground controls. Temperature and relative humidity rarely exceeded the maximum recommendations for storage in the Shuttle and ISS, suggesting that radiation exposure and the long-term storage anticipated during exploration missions are more likely to be responsible for any pharmaceutical degradation (Du et al., 2011). Although pharmaceutical degradation possibly due to radiation exposure at low Earth orbit has been addressed by past research projects reported in the literature (Du et al., 2011; Putcha et al., 2011); these environments don't adequately capture the chemical and physical changes that may occur with exposures to the radiation environment outside the Earth's magnetic sphere. Therefore, it is unknown how radiation in deep space will affect the degradation rates of medications in an exploration mission formulary.

Gamma irradiation has been used as a method of microbial sterilization in the food, medical device, and to a lesser extent, pharmaceutical industries. However, the use of gamma irradiation on pharmaceutical products can result in a loss of active pharmaceutical ingredient (API) potency, the creation of radiolysis byproducts, and a reduction of the molecular weight of polymer excipients, and can influence drug release from the final product. Despite these risks, use of gamma sterilization has continued to increase and demonstrate strong applicability to a wide range of pharmaceutical products. The increased interest in this technique is likely the result of the discovery of new insights into compatibility of some pharmaceutical products with radiation, and optimization of the radiation dose and environmental conditions to limit product degradation during sterilization. A recent literature review article (Hasanain et al., 2014), summarizing utility and feasibility of gamma sterilization in the pharmaceutical industry, discussed how potentially harmful high ionization energy from gamma irradiation can be harnessed and optimized by formulation changes (i.e. addition of radioprotectants), or by varying the

irradiation conditions (temperature, product state, oxygen environment, dose, and dose rate). The advancements made in gamma sterilization research may have further application for pharmaceutical products used during an exploration spaceflight mission. However, the potential damage and subsequent solutions for these products when they are exposed to the forms of ionizing radiation found in deep space (i.e. galactic cosmic rays, solar energetic particles), may be considerably different from damage resulting from gamma sterilization and solutions to prevent or counteract such damage. Ideally, stability studies would be capable of characterizing quality, chemical integrity, and safety of medications exposed to the deep-space environment. However, in the absence of obtaining those characterizations from deep-space exposure, a close environmental analog such as the ISS or targeted radiation exposure could reveal additional insight that could bring us closer to that safe and effective exploration mission medication formulary.

Medications that are unlikely to remain safe and effective throughout the exploration mission duration will be considered for stability testing. Stability testing is terrestrially required to demonstrate that a pharmaceutical product meets its acceptance criteria throughout its shelf life and to gain regulatory approval for commercialization. The purpose of stability testing is to provide evidence of how the quality of a drug substance or formulated drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a shelf life for the drug product and recommended storage conditions (ICH Q1A R2, 2003). Stability testing is costly in terms of resources and time; therefore the above prioritization steps will be taken before any medications are considered. However, the opportunity to perform well designed stability studies in the past has been limited by the lack of matching controls for comparing stability test results with flight medications.. This will be addressed by ensuring that matching control medications are available for those prioritized medications retrieved from spaceflight; thereby enabling control-based drug stability analysis.

A stability study is a designed experiment in which the pharmaceutical product is stored in environmental chambers and followed for a prescribed amount of storage time. Periodically the product is sampled to measure a series of stability-limiting properties. During a stability study, testing processes are developed to evaluate pharmaceutical quality attributes, such as API identity, concentration, and purity. Additionally, the capability of a particular finished dosage form in a specific container/closure system to remain within its physical, chemical, microbiological, toxicological, protective, and informational specifications are defined (Kommanaboyina et al., 1999). Any changes to those drug properties beyond the accepted criteria could risk patient safety, as by delivering a less than efficacious dose or toxic degradation products (Huynh-Ba, 2009). The Food and Drug Administration (FDA) requires that pharmaceutical companies determine a time limit within which they can guarantee the full potency and safety of medications. This time limit, or shelf life, is typically 1-2 years from the medication manufacture date if the product remains stored in the original unopened container, under optimal environmental conditions. A drug product's shelf life or expiration dating period is defined as the time period during which that drug product is expected to remain potent within approved specifications, provided that it is stored under the conditions defined by

the manufacturer on the container label [FDA Guidance for Industry Q1A(R2)]. Degradation reactions like oxidation, reduction, hydrolysis, or racemization can play a vital role in stability of a pharmaceutical product, and depend on conditions such as concentration of reactants, pH, radiation, and presence of catalysts. A finished pharmaceutical product may also undergo changes in appearance, consistency, content uniformity, clarity, moisture contents, particle size and/or shape, pH, or package integrity, which may be a result of impact, vibration, abrasion, or environmental factor fluctuations and may cause the product to require further testing processes and evaluations (such as tests for tablet hardness, friability, dissolution, and diffusion). Therefore, it is possible that the conditions of deep spaceflight may still affect the labeled shelf life of medications even when they are sealed in their original manufactured packaging. Planetary exploration missions include DRMs that have timelines in excess of 2.5 years for total mission duration. Given a lack of ability to resupply these missions, it may be necessary to perform stability studies with selected high-priority medications that appear unlikely to last the full mission duration.

Shelf life determined by stability testing can be expensive and time-consuming. Ideal ground-based analogs mimicking the environmental conditions of exploration missions are unavailable; therefore, predictive stability modeling methodologies that offer statistically accurate estimations should also be considered. Statistical models are mathematical descriptions of how the data are produced and how they vary from observation to observation (Littell et al., 2006). The Product Quality Research Institute (PQRI) Stability Shelf Life Working Group (SSLWG), a collaborative involving experts from FDA's Center for Drug Evaluation and Research, the pharmaceutical industry, and academia, was established in late 2006 to investigate current and alternative statistical methods for estimating the shelf life of pharmaceuticals from stability data. The PQRI SSLWG developed a modeling context that could be extended to linear or nonlinear regression over time, and is guided by three premises: (1) the two primary processes giving rise to observations are variation among batches, and changes in a batch over time; (2) the observed response is a function of these two processes; and (3) following ICH guidance, changes over time follow a linear regression (Stroup and Quinlan, 2010). So far, Stroup and Quinlan have characterized five methodologies to estimate pharmaceutical shelf life. Statistical modeling techniques may prove to be useful tools for predicting shelf life of pharmaceutical formulary candidates for exploration spaceflight.

Deliverables for answering Critical Question 2

Data Mining

1. Element Directed: A catalogue of labeled shelf lives for selected medications in their original manufactured packaging
2. A list, based on information provided by the manufacturer and scientific literature, consisting of proposed medications that are verified to maintain labeled shelf life in original packaging

Ground-based Stability Studies

1. Element-directed or solicited ground-based pharmaceutical stability studies as needed to characterize the robustness of medications from the list of selected therapeutic classification drug candidates (end of 2nd Q, FY17).
    a. Medications will be selected on the basis of prioritization and retrieved from ISS down-mass, to provide opportunities for ground analysis.
    b. Sufficient medications will be procured as needed to provide matching (identical manufacturer and lot) control samples to support ground-based pharmaceutical stability stress testing and analytical identification with portable assessment technology.
2. Stability reports characterizing shelf life of tested drugs, and results of all physical and chemical stability tests (within 1-2 years of award, contingent on award criteria).
    a. These reports will be produced by stability studies to maximize effort, time, and resources, there will be no duplication of study drugs between directed and solicited investigational sites.

Shelf Life Estimation / Predictive Modeling Studies

1. Element-directed and solicited studies employing predictive stability modeling programs (i.e. linear, nonlinear, or quantile regression modeling programs), to statistically estimate shelf life of selected medications from the list of the selected therapeutic classification drug candidates to aid in the identification of the most robust medications (end 2nd Q FY17)
2. Predictive reports, produced by these studies, with shelf life estimation results for all medications tested (within 1-2 years of award, contingent on award criteria)

Critical Question 3: Of the medications that do not remain stable for the full mission duration, can we characterize their likely effective shelf life on a specific DRM?

a. Are there medications that don't have a shelf life problem if they stay in the original packaging?

b. If so, how much extra volume and mass does keeping the original packaging add?

For different DRMs the answer to Critical Question 2 above will depend on the expiration dates of the medications in the original packaging. Proposed medications for the exploration formulary will be assessed, and known information about medication expiration durations will be catalogued and compiled into a list. Should selected medications identified as being able to last for the duration of an exploration spaceflight journey require an operational need for repackaging, reevaluation would be needed to establish a shelf life beyond the required one year from the repackaging date. This list of medications that require reevaluation can be even further reduced and prioritized to limit

expenditure of research resources. This approach of reduction and prioritization will rely on available evidence extracted from the literature and shelf life data provided by manufacturers for the proposed formulary therapeutic classifications or specific medications under consideration.

Deliverables for answering Critical Question 3

1. Element Directed: A feasibility assessment of proposed exploration spaceflight formulary medications, conducted by the operational pharmacy at Johnson Space Center to determine which medications can be made available in their manufactured packaging for exploration spaceflight missions.
2. A report distinguishing those medications that can be flown in original manufactured packaging from those that cannot, provided by the operational pharmacy.

Critical Question 4: Can we provide the crew a way to determine in real time whether a medication is chemically stable, still active, or degraded?

Standard methods for pharmaceutical analysis to determine API content involve the use of high- and/or ultra-performance liquid chromatography (HPLC/UPLC). This technique requires destruction of the samples by extraction of the API into organic solvent mixtures and water. Currently, nondestructive optical spectroscopy methods such as infrared and Raman spectroscopy are being used for chemical structural identification of drugs by the pharmaceutical industry. For over a decade handheld Raman technology was used to monitor purity of pharmaceutical raw materials, providing rapid information about the chemical structure and related physical or biopharmaceutical properties of all types of pharmaceutical dosage forms. Handheld Raman devices with both qualitative and quantitative capabilities are being developed for more comprehensive spectroscopic analyses of pharmaceuticals. Researchers from the U.S. Food and Drug Administration have demonstrated that the transfer of a spectral library and chemometric-based Raman methods across different Raman handheld devices is feasible (Hajjou and Lukulay, 2014). Infrared spectroscopy is a versatile method for fingerprinting and identification of pharmaceutical compounds and functional groups within molecules. It measures energy absorption across the infrared frequency range. Gas, liquid, or solid pharmaceutical samples can be analyzed by infrared spectroscopy. The Fourier transform infrared (FTIR) spectroscopic method allows simultaneous analysis across the infrared frequency range. Due in part to its speed and sensitivity, FTIR has become the standard of pharmaceutical infrared spectroscopic analysis. Technological advances over the past two decades in areas such as lasers, batteries, software, and micro electromechanical systems (MEMS) now allow manufacturers to routinely design and build rugged, compact, portable FTIR instruments whose performance is the same or even better than that of benchtop systems. This rapidly evolving technology provides nondestructive analytical capabilities that would optimize care during exploration missions.

Deliverables for answering Critical Question 4

1. Element-directed or solicited proof-of-concept studies designed to validate utility for exploration missions of novel commercial off-the-shelf (COTS) portable technology designed to perform nondestructive, real-time assessment and characterization of chemical integrity and active pharmaceutical ingredient content available in medications (end 2nd Q FY17)
    a. Raman spectroscopy (Hajjou and Lukulay, 2014)
    b. Fourier transform infrared (FTIR) spectroscopy (Matkovic et al., 2005)
    c. Miniature mass spectrometer (Keil et al., 2007)
    d. Portable GC/MS (Biemann et al., 1976; Gloeckler et al., 1995)
2. The medications analyzed are identical (matching manufacturer and lot) to those tested by the ground-based pharmaceutical stability stress tests.
3. A report from each study summarizing proof of concept for each device evaluated, assessment and characterization of chemical integrity and API content available in the medications tested, and a feasibility assessment for exploration utility (within 1-2 years of award, contingent on research award timeline).
4. Comparison of results with those obtained by standard liquid chromatographic (HPLC / UPLC) analyses for validation (end of 2nd Q FY18 or FY19, contingent on research award timeline).
5. Exploration of customized development leading to a more robust device able to withstand the harsh spaceflight environment (e.g microgravity), assess multiple drug classes, and modular in that we can add to the spectral library.

Formulary Safety and Toxicity

Critical Question 5: As the formulary medications degrade,

a. will they become toxic?

b. will they remain safe and effective?

Once the prospective formulary for exploration is selected, it may be desirable to establish the chemical and physical stability of selected medication compounds, as well as their safety, by identifying degradation profiles and products. The formation of toxic degradation products is a potentially critical quality and patient safety issue for exploration mission formulary medications. It is important to determine whether degradation products are therapeutically active, characterize the activity, and evaluate the toxicity profile for degradation products of each formulary medication. A well- designed in vivo toxicology study would include exposing a suitable animal model to degraded medications or isolated degradation products of a selected medication to ascertain drug safety profiles. Although the pharmacokinetics of toxic drug degradation products may have an impact on product safety, these data are frequently unavailable. Traditionally, evaluation of the safety of new chemicals and pharmaceuticals requires regulatory studies in animals,

designed to protect human health and the environment. Generally, risk assessment can be viewed as a process by which information from various sources (e.g. in vitro, in silico, and in vivo studies) is combined to characterize a particular chemical or molecular entity. Ideally, chemical and drug development would be front-loaded with experiments that can definitively select safe compounds as quickly as possible. Three-dimensional (3D) cell and tissue models bring us ever closer physiologically to the in vivo situation. The incentive to use novel in vitro methods is high because being able to manipulate the test system is advantageous, as it may provide a more thorough understanding of potential mechanisms of toxicity and the human and animal response to exposure to foreign chemicals. Another novel approach for product risk assessment incorporates the prediction capability of physiologically based pharmacokinetic (PBPK) models into a rational drug degradation risk-assessment procedure using a series of model drug degradants (substituted anilines). The PBPK models are parameterized using a combination of experimental and literature data, and computational methods. Relative to traditional risk-assessment calculations, this novel PBPK approach seems to provide a rational basis for drug instability risk assessment by focusing on target tissue exposure and leveraging physiological, biochemical, and biophysical knowledge of compounds and anatomy and physiology of the targeted animal model species. As data accumulate to support the predictive validity of in silico and in vitro studies for human safety, these techniques will enable compounds to be deselected earlier in development, thereby limiting the need for animal testing (Chapman et al., 2013).

Deliverables for answering Critical Question 5

Toxicity Studies

1. Studies (in vivo and/or in vitro) directed or solicited on an as-needed basis to identify degradation profiles of selected medications from the targeted therapeutic classifications proposed for the exploration space medical kit formulary. Determination of whether degradation products are therapeutically active, characterization of the activity, and evaluation of the toxicity profile for degradation products (3rd Q FY17).
2. Reports, delivered by studies, that summarize results of toxicity studies including identified and characterized degradation and toxicity profiles of the selected medications from the targeted therapeutic classifications (The bolded text indicates major milestones, as defined in previous versions, since deleted. Can remove, to be consistent with new format). (1-2 years post initiation – 3rd Q FY18, Y19, in accordance with award timeline).
3. As needed, identification of an ideal animal model and solicitation or direction of in vivo toxicology animal (flight and/or ground) studies using degraded medications or isolated degradation products from the selected medications to ascertain drug safety profiles (initiate 1st Q FY20).
4. Reports, delivered by studies, that summarize results of in vivo animal model toxicity studies and include defined safety profiles of the tested selected medications from the targeted therapeutic classifications (1-2 years post initiation – 1st Q FY21, or FY22, in accordance with award timeline).

5. A final list of tested medications now verified as safe will be recommended to be considered as the target Core medication formulary for exploration missions (by FY2022).

Dosing Monographs

1. For select degraded medications with reduced API, but verified as safe, incorporation of degradation and safety profiles from previous work to identify modeling technology with the capability to generate dosing monographs adjusted for decreasing API content (initiate 1st Q, FY22).
2. Studies directed and/or solicited as needed to generate dosing monographs adjusted for decreasing API content, using identified modeling technology, and degradation and safety profile results from previous studies (2nd Q, FY22).
3. Reports, delivered by studies, that include recommended dosing monographs for medications with reduced API but verified as safe (VAS), selected from the targeted therapeutic classifications list (by end of 2nd Q, FY2024).

Novel Technology and Innovation

Critical Question 6: Do alternative methods exist for supplying formulary medications for a DRM?

Critical Question 7: Can we modify existing properties of pharmaceuticals to minimize their resource footprint or improve their tolerance to the spaceflight environment?

As society's demands for safe and efficacious medications grow, technological solutions have become essential to reducing barriers to clinical success. Technology can contribute to a research plan for exploration missions by helping to provide better target selection and validation of disease pathophysiology, identifying more predictive and biologically relevant high-throughput assays, and acquiring pharmacology and toxicology data early, thereby eliminating time and resources expended on formulary candidates with poor safety profiles. Pharmaceutical interventions, including sustained and targeted delivery technologies such as controlled-release topical, subcutaneous, intranasal, and inhalation dosage forms, may provide for exploration missions the preventive health care solutions that are not currently addressed by standard pharmaceutical care (Putcha et al., 2011).

In recent years, considerable research has been done on preparing materials and finding new uses for nanoscale structures in drug delivery. Uses such as carriers for controlled and targeted drug delivery, micro patterned devices, and systems for biological recognition have demonstrated the versatility of these materials (Langer, 2003). Nanostructures also have the abilities to protect drugs encapsulated within them from physiologic degradation and to target their delivery with sustained release, and they are suitable for oral administration (Ochekpel et al., 2009). Nanotechnology has proven

capable of revolutionizing most areas of technology critical to NASA's future missions (Baker Institute Policy Report, 2012). Promising ideas for novel therapeutic intervention for pharmaceuticals, medical imaging and diagnostic capabilities, and implant and tissue regeneration materials offer opportunities to improve astronaut health management and provide solutions for many of clinical medicine's unsolved problems. University College London scientists demonstrated the feasibility of fused-filament 3D printing (FF 3DP) to fabricate drug-loaded tablets and have shown that the release profiles obtained can be modified by careful selection of the printing parameters. The results immediately suggest that FF printing could offer a new method of manufacturing for personalized-dose medications and/or for tablets prepared at the point of use (Goyanes et al., 2014).

Deliverables for answering Critical Questions 6 and 7

Pharmaceutical Performance Enhancement

1. Technology Watch Element Directed (initiated 1st Q FY17, ongoing). Exploration of novel drug development techniques, dosage forms, and delivery systems for the selected formulary medications, with the goal of improving stability, pharmacokinetic, and pharmacodynamic outcomes (Pharmacotherapeutics Discipline Research Pharmacist, Potomac Institute).
    a. Dosage form and delivery platforms (Including but not limited to the following): nanotechnology, gene therapy, and biomaterials (Edelhauser et al., 2010; Putcha et al., 2011; Langer and Peppas, 2003; Ochekpe et al., 2009; Baker Institute, 2012; Seigneuric et al., 2010; Sajja et al., 2009; Felnerova et al., 2004; Pridgen et al., 2013; Hoare and Kohane, 2008; Peppas, 2005).
    b. Three-dimensional (3D) printing technology (Goyanes et al., 2014). Different types of complex oral drug delivery devices have been fabricated using the 3DP process: immediate-extended release tablets, pulse release, breakaway tablets, and dual pulsatory tablets (i.e. diclofenac sodium).
2. Annual report summarizing promising technology that could enhance the space exploration medication formulary, submitted by the Pharmacotherapeutics Discipline (Research Pharmacist) (annually, starting 1st Q, FY18).

Technology Proof of Concept

1. Element-directed or solicited proof-of-concept studies for COTS drug formulations, devices, drug development platforms, and delivery systems (1st Q FY18).
2. Reports, delivered by studies, that summarize proof of concept for each COTS drug formulation, device, drug development platform, and delivery system evaluated, including feasibility assessment for exploration utility (1st Q, FY19 or 20, as defined by award timeline).

Pharmacokinetic / Pharmacodynamic Studies

1. Element-directed or solicited comparative PK / PD studies using novel dosage forms or delivery platforms of medications selected from the prioritized lists developed from targeted therapeutic classifications to verify superior performance (1st Q, FY17)
2. Studies will deliver a report summarizing results of comparative PK/PD studies (1st Q, FY19 or 20, as defined by award timeline).
3. Recommendation of promising products for further testing as prospective candidates for the exploration mission formulary (2nd Q, FY20).

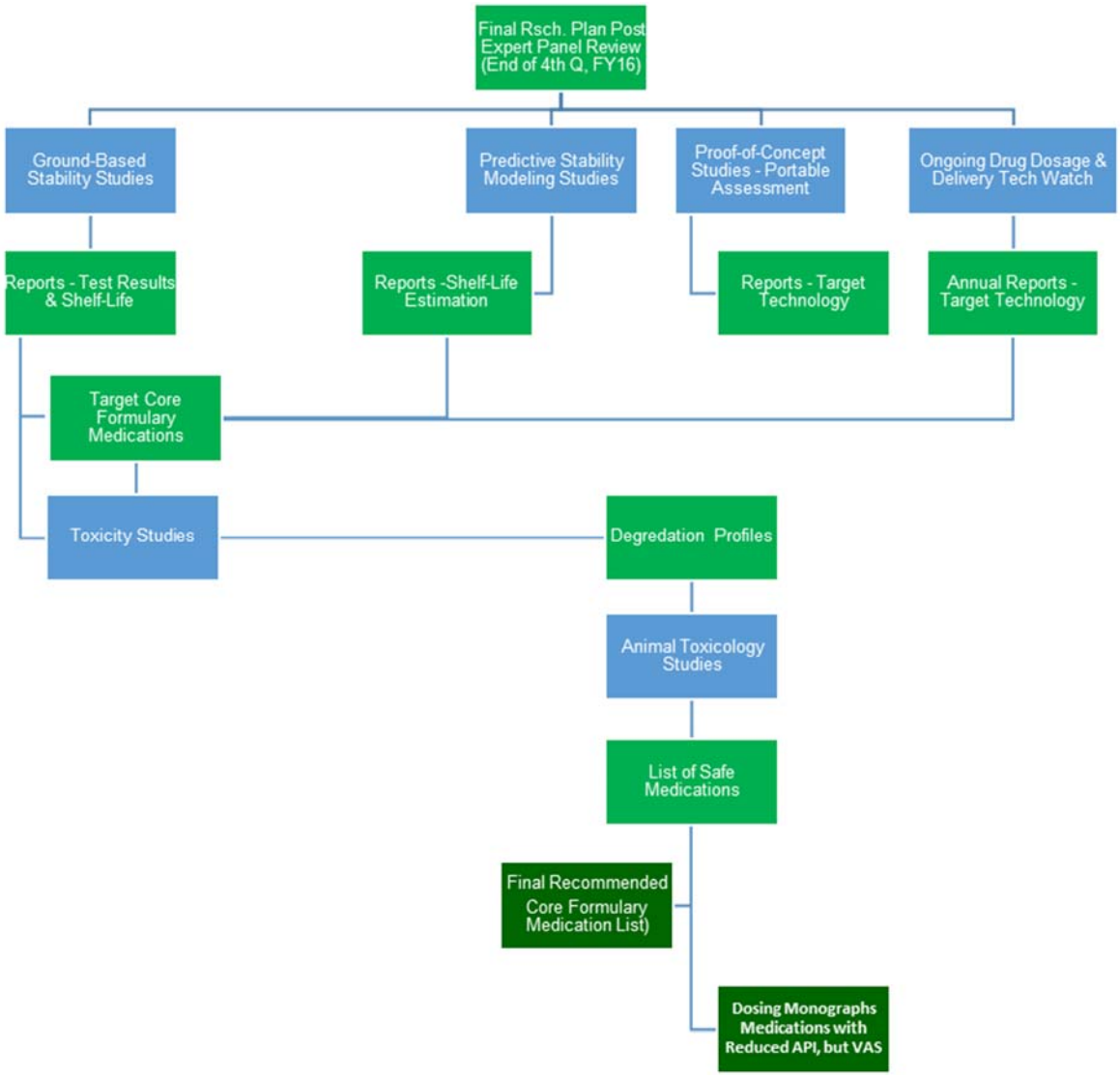

***Figure 4.0**: Visual description of the proposed ExMC Med02 "Pharmacy" Gap projects (blue boxes) illustrating non-sequential or grouped project relationships, and highlighting significant deliverables (green boxes).*

References

1. Institute of Medicine, Technical Report, Committee on Creating a Vision for Space Medicine during Travel beyond Earth Orbit, February 22, 2001, Johnson Space Center, Houston.
2. Du B, Daniels VR, Vaksman Z, Boyd JL, Crady C, Putcha L. Evaluation of physical and chemical changes in pharmaceuticals flown on space missions. AAPS J. 132:299-308, 2011.
3. Wotring VE. Medication use by U.S. crewmembers on the International Space Station. FASEB J. 29(11):4417–4423, 2015.
4. Wotring VE. Chemical potency and degradation products of medications stored over 550 Earth days at the International Space Station. AAPS J. 18(1):210–216, 2016.
5. Barger LK, Flynn-Evans EE, Kubey A, Walsh L, Ronda JM, Wang W, Wright KP, Czeisler CA. Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: An observational study. Lancet Neurol. 13(9):904–912, 2014.
6. Basner M, Dinges DF. Lost in space: Sleep. Lancet Neurol. 13(9):860–862, 2014.
7. Billica, R. 2000. In-flight Medical Events for US Astronauts during Space Shuttle Program STS-1 through STS-89, April 1981–January 1998. Presentation to the Institute of Medicine Committee on Creating a Vision for Space Medicine During Travel Beyond Earth Orbit, February 22, Johnson Space Center, Houston.
8. Hall KL, Vogel AL, Stipleman BA, Stokols D, Morgan G, Gehlert S. A four phase model of translational team-based research: Goals, team processes, and strategies. Transl Behav Med. 2:415–430, 2012.
9. Woolf SH. The meaning of translational research and why it matters. JAMA. 299(2): 211–213, 2008. doi:10.1001/jama.2007.26. PMID 18182604.
10. NASA, JSC-65722 Rev. B. Space Medicine Exploration Medical Condition List, 2012.
11. Keiser MJ, Setola V, Irwin JJ, Laggner C, Abbas AI, Hufeisen SJ, Jensen NH, Kuijer MB, Matos RC, Tran TB, Whaley R, Glennon RA, Hert J, Thomas KL, Edwards DD, Shoichet BK, Roth BL. Predicting new molecular targets for known drugs. Nature. 462(7270):175–181, 2009.
12. Atias N, Sharan R. An algorithmic framework for predicting side effects of drugs. J Comput Biol. 18(3):207-218, 2011.
13. Pauwels E, Stoven V, Yamanishi Y. Predicting drug side-effect profiles: A chemical fragment-based approach. BMC Bioinformatics. 18(12):169, 2011.
14. Scheiber J, Jenkins J, Sukuru S, Bender A, Mikhailov D, Milik M, Azzaoui K, Whitebread S, Hamon J, Urban L, Glick M, Davies J. Mapping adverse drug reaction in chemical space. J Med Chem. 52(9):3103–3107, 2009.
15. Hasanain F, Guenther K, et al. Gamma sterilization of pharmaceuticals-A review of the irradiation of excipients, active pharmaceutical ingredients, and final drug product formulations. PDA J Pharm Sci Technol. 68(2):113-137, 2014.
16. Kommanaboyina B, Rhodes CT. Trends in stability testing with emphasis on stability during distribution and storage. Drug Dev Ind Pharm 25:857- 867, 1999.
17. Huynh-Ba K (Editor). Handbook of Stability Testing in Pharmaceutical Development: Regulations, Methodologies, and Best Practices. [Springer], 2009.

18. International Conference on Harmonization. ICH Q1A (R2): Stability Testing of New Drug Substances and Products. Step 5. Rockville, MD: U.S. Food and Drug Administration, 2003.
19. Littell RC, Milliken GA, Schabenberger O, Stroup WW, Wolfinger RD. SAS for Mixed Models, 2nd ed. Cary, NC:SAS Institute, Inc., 2006.
20. Stroup W, Quinlan M. Alternative shelf life estimation methodologies. In: Joint Statistical Meeting Proceedings, Biopharmaceutical Section. Alexandria, VA: American Statistical Association. pp. 2056–2066, 2010.
21. Hajjou M, Lukulay P. Potential use of handheld Raman devices as tools for screening medicines for quality. BioPharma Asia. January/February 2014:14-21, 2014. http://www.usp.org/sites/default/files/usp, pdf/EN/pubs-potential_use_of_handheld_raman_devices-biopharma_asia-jan-feb_2014.pdf (accessed August 18, 2016).
22. Matkovic SR, Valle GM, Briand LE. Quantitative analysis of ibuprofen in pharmaceutical formulation through FTIR spectroscopy. Lat Am Appl Res. 35:189–195, 2005.
23. Keil et al, Ambient mass spectrometry with a handheld mass spectrometer at high pressure. Anal Chem. 79:7734-7739, 2007.
24. Biemann K, Oro J, Toulmin P 3rd, Orgel LE, Nier AO, Anderson DM, Simmonds PG, Flory D, Diaz AV, Rushneck DR, Biller JA. Search for organic and volatile inorganic compounds in two surface samples from the Chryse Planitia Region of Mars. Science. 194:72−76, 1976.
25. Gloeckler G, Balsiger H, Burgi A, Bochsler P, Fisk LA, Galvin AB, Geiss J, Gliem F, Hamilton DC, Holzer TE, Hovestadt D, Ipavich FM, Kirsch E, Lundgren RA, Ogilvie KW, Sheldon RB, Wilken B. The Solar Wind and Suprathermal Ion Composition Investigation on the Wind Spacecraft. . Space Sci Rev. 71:79−124, 1995.
26. Edelhauser HF, Rowe-Rendleman CL, Robinson MR, et al. Ophthalmic drug delivery systems for the treatment of retinal diseases: Basic research to clinical applications. Invest Ophthalmol Vis Sci. 51(11):5403-5420, 2010. doi:10.1167/iovs.10-5392.
27. Putcha L, Taylor PW, Boyd JL. Biopharmaceutical challenges of therapeutics in space: formulation and packaging considerations. Ther Deliv. 2(11):1373-1376, 2011.
28. Langer R, Peppas NA. Advances in biomaterials, drug delivery and bionanotechnology. AIChE J. 49(12):2990-3006, 2003. doi:10.1002/aic.690491202.
29. Ochekpe, NA, Olorunfemi PO, Ngwuluka NC. Nanotechnology and drug delivery part 1: Background and applications. Trop J Pharm Res 8(3):265–274, 2009.
30. Baker Institute Policy Report. NASA's Relationship with Nanotechnology: Past, Present, and Future Challenges. Rice University, Num. 54, Oct. 2012. ISSN 1941-6466.
31. Seigneuric R, Markey L, Nuyten DS, et al. From nanotechnology to nanomedicine: Applications to cancer research. Curr Mol Med. 10(7):640– 652, 2010.
32. Sajja HK, East MP, Mao H, et al. Development of multifunctional nanoparticles for targeted drug delivery and noninvasive imaging of therapeutic effect. Curr Drug Discov Technol. 6(1):43–51, 2009.
33. Felnerova D, Viret JF, Gluck R, et al. Liposomes and virosomes as delivery systems for antigens, nucleic acids and drugs. Curr Opin Biotechnol. 15:518–529, 2004.

34. Pridgen EM, Alexis F, Kuo TT, et al. Transepithelial transport of Fc-targeted nanoparticles by the neonatal fc receptor for oral delivery. Sci Transl Med. 5(213):213ra167, Nov. 2013.
35. Hoare TR, Kohane DS. Hydrogels in drug delivery: Progress and challenges. Polymer. 49:1993-2007, 2008.
36. Peppas NA. Smart Drug Delivery and Bionanotechnology. Center for Biomaterials, Drug Delivery, Bionanotechnology and Molecular Recognition. 2005.
37. Goyanes A, Buanz AB, Basit AW, Gaisford S. Fused- filament 3D printing (3DP) for fabrication of tablets. Int J Pharm. 476(1–2):88-92, 10 December 2014. ISSN 0378-5173.